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ORIGINAL ARTICLE

Acute rotavirus gastroenteritis in children less than 5 years old: Salient clinical and laboratory features

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Abstract

Background: Rotavirus is one of the most common etiological agents that can cause gastroenteritis in young children in many countries worldwide, including Malaysia. The objective of the study was to determine the clinical and laboratory features of acute rotavirus gastroenteritis in children aged less than 5 years. *Materials and Methods:* This retrospective study involved paediatric patients warded in a tertiary medical centre in Kuala Lumpur for acute gastroenteritis from 2015 to 2022. Data for these children were obtained from the hospital's electronic medical records and online laboratory management system. *Results:* Out of a total of 177 patients, 30.5% (54/177) were diagnosed with rotavirus gastroenteritis (RG) and 69.5% (123/177) with non-rotavirus gastroenteritis (NRG). Children with RG were more likely to have vomiting compared to those with NRG (85.2% vs. 68.3%; p=0.026). Dehydration was also significantly associated with RG (64.8% vs. 43.9%; p=0.014). However, RG was less likely to be associated with fever (57.4% vs. 76.4%; p=0.013) and convulsions (0.0% vs. 8.1%; p=0.033). The blood C-reactive protein (CRP) mean and SD in RG were lower (0.86 ± 0.81 vs. 4.26 ± 2.71 mg/L; p=0.001), while the serum urea mean and SD in RG were higher (4.94 ± 3.05 vs. 3.87 ± 2.22 mmol/L; p=0.009). *Conclusion:* Despite shared features, RG can be distinguished from NRG based on the presence or absence of vomiting, dehydration, fever and convulsions, as well as the extent of elevation in the serum urea and blood CRP levels.

Keywords: rotavirus, gastroenteritis, fever, dehydration, vomiting, C-reactive protein, urea

INTRODUCTION

It has been half a century since rotavirus was first described as a human pathogen in children with gastroenteritis, although it was initially discovered in monkeys back in the 1950s.[1] Its name originates from the Latin word "rota" (which translates to "wheel") because under the electron microscope, the virus has a wheel-like appearance. Today, despite the availability of effective vaccines, rotavirus is still the most prevalent infectious agent responsible for severe diarrhoea in both developed and developing nations.[2] Worldwide, rotavirus causes >250 million cases of infectious diarrhoea in children below the age of five years, and it accounts for up to 50% of childhood hospitalisations due to diarrhoea.[3,4] Also, it has the unenviable distinction of being the third leading pathogen responsible for the death of children from this age group, with >200,000 deaths being reported annually.[1,4] Since the virus is transmitted via the fecal-oral route, the 4 Fs (i.e. tainted food, contaminated fluid, unsanitary formites and "dirty fingers") are the major sources of infection, particularly in children day-care centres.[1]

Such is the importance of rotavirus that each child experiences at least one episode of rotavirus gastroenteritis (RG) by the age of five years.[5] Fortunately, even though children can be infected by the virus repeatedly, the severity of the infection progressively diminishes as specific immunoglobulin A (IgA) antibodies are produced.[6] The infection can vary from a

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mild watery diarrhoea to a severe dehydrating diarrhoea that is fatal.[1] Additionally, a rotavirus infection can also induce fever and vomiting, with the latter being a hallmark of the infection, further aggravating dehydration and hindering the effectiveness of oral rehydration therapy.[6] The objective of this study was to ascertain if there were any clinical features accompanying childhood gastroenteritis that were more likely to be associated with RG. In addition, this study sought to determine if there were any laboratory parameters that were more likely to be abnormal in RG. The ability of being able to predict which child with gastroenteritis has a higher likelihood of RG would ensure more targeted treatment and attention by healthcare workers.

MATERIALS AND METHODS

Research design

This retrospective study involved paediatric patients warded for acute gastroenteritis (AGE) in Hospital Canselor Tuanku Muhriz (HCTM), Kuala Lumpur, Malaysia from 2015 to 2022. Ethical approval was obtained from the Research Ethics Committee of the National University of Malaysia (reference code: UKM PPI/111/8/JEP-2023-203). Convenience sampling was used.

The inclusion criteria were the availability of a stool rotavirus antigen test result, aged not more than five years at the time of admission and had experienced AGE symptoms for a duration not exceeding two weeks. Children on diuretic therapy, those with preexisting comorbidities (e.g., inflammatory bowel disease, coeliac disease, malignancy, metabolic disease, renal failure and cardiac disease) or bilious emesis/bowel obstruction were excluded from analysis. Children with incomplete clinical data were also excluded.

Data Collection

The data collected from the children's electronic medical records included age, sex, underlying medical condition (to facilitate exclusion from analysis) and presenting clinical characteristics. The specific characteristics we focused on were diarrhoea, vomiting, dehydration, fever, reduced oral intake, convulsions, lethargy, upper respiratory symptoms, abdominal pain and abdominal distension. Laboratory results such as the full blood count (consisting of haemoglobin level, haematocrit, total white cell count, platelet count, neutrophil percentage and lymphocyte percentage), renal profile (encompassing serum sodium, potassium, urea and creatinine levels) and C-reactive protein level (CRP) were retrieved from the hospital's online laboratory management system. Children with RG were those who were assigned the International Classification of Diseases, Tenth Revision (ICD-10) code A08.0 at discharge. Statistical analysis was performed using the SPSS Statistics software version 28 (IBM, USA). Any probability value (p-value) of 0.05 and below was considered statistically significant.

RESULTS

A total of 177 patients fulfilled our inclusion criteria. Out of these, 30.5% (54/177) were diagnosed with acute RG and 69.5% (123/177) had acute non-rotavirus gastroenteritis (NRG). The median age was 12 months for patients with RG and 14 months for those with NRG. Boys made up 50% (27/54) of the RG and 43.9% (54/123) of the NRG cases, although this was not statistically significant.

Table 1 shows the clinical characteristics of RG and NRG. The single most common symptom for each type of AGE was diarrhoea, with approximately 93% of children experiencing it. However, there was no statistically significant association between diarrhoea and RG. There was, however, a statistically significant association between vomiting and RG – vomiting occurred with a frequency of 85% and 68% in RG and NRG, respectively. Children with RG were also more likely to experience dehydration (65% vs 44%) and this association was statistically significant.

In NRG, fever was a statistically significant clinical characteristic with a frequency of 76%, while it was only present in 57% of children with RG. Also, 8% of children with NRG experienced convulsions, while no children with RG experienced it, resulting in a statistically significant association between NRG and convulsions. No statistically significant association was seen with the other clinical characteristics (i.e., abdominal distension, abdominal pain, poor oral intake, lethargy and upper respiratory tract symptoms).

Table 2 shows the laboratory profile of patients with RG and NRG. The mean CRP level was significantly higher for NRG compared with that for RG. Conversely, the mean serum urea level for RG was significantly higher compared with that for NRG. No statistically significant difference between the means for the other laboratory parameters was noted.

TABLE 1: Clinical characteristics of children with acute gastroenteritis

Clinical characteristic	Rotavirus gastroenteritis (n=54)	Non-rotavirus gastroenteritis (n=123)	p-value*
Diarrhoea	50 (92.59%)	114 (92.68%)	1.000
Vomiting	46 (85.19%)	84 (68.29%)	0.026
Dehydration	35 (64.8%)	54 (43.9%)	0.014
Fever	31 (57.41%)	94 (76.42%)	0.013
Convulsions	0 (0.00%)	10 (8.13%)	0.033
Poor oral intake	41 (75.93%)	98 (79.67%)	0.559
Lethargy	13 (24.07%)	23 (18.70%)	0.423
URTI symptoms	5 (9.26%)	20 (16.26%)	0.251
Abdominal pain	5 (9.26%)	9 (7.32%)	0.763
Abdominal distension	0 (0.00%)	3 (2.44%)	0.554

All data are displayed as no. (%); URTI, upper respiratory tract infection.
* Derived from Fisher's exact test

DISCUSSION

In Asia, it is estimated that 45% of admissions due to AGE in children younger than 5 years is attributed to rotavirus.[8] However, our data revealed a much lower figure of 30.5%. The reason for this discrepancy is the wide region-to-region variation in disease burden, even within the same country. For instance, a region in Indonesia named Bandung reported a stool rotavirus positivity rate of 68.15%, while another Indonesian region (i.e., Central Jawa) reported a rate of only 6.37%.[2] Malaysia's stool rotavirus positivity rate also varied between 16% in Kota Kinabalu to 54% in Penang, with a national average of 30.3%.[7] Thus, our positivity rate is consistent with the national average. In our study, the median age of patients with RG was 12 months – this figure is consistent with that reported by an Indian study, in which 78.3% of children with rotavirus diarrhoea were aged between 6-15 months.[9] A possible explanation for the lower prevalence of rotavirus cases in children younger than 6 months is the presence of protective maternal IgA antibodies in the gut of these children as a result of breastfeeding.[10] As breastfeeding frequency diminishes with

TABLE 2: Laboratory profile of children with acute gastroenteritis

Laboratory parameter	Rotavirus gastroenteritis	Non-rotavirus gastroenteritis	p-value*
Haemoglobin (g/dL)	12.17 ± 1.25	11.82 ± 1.53	0.133
Haematocrit (%)	36.44 ± 3.88	35.61 ± 4.33	0.251
Platelet count ($x10^9$/L)	408.94 ± 142.07	377.50 ± 121.06	0.135
White cell count ($x10^9$/L)	11.90 ± 4.89	14.28 ± 22.95	0.452
Neutrophils (%)	52.96 ± 21.94	54.61 ± 20.33	0.636
Lymphocytes (%)	34.90 ± 18.41	33.25 ± 16.58	0.564
CRP (mg/dL)	0.86 ± 0.81	4.26 ± 2.71	0.001
Sodium (mmol/L)	136.67 ± 3.83	135.66 ± 3.26	0.077
Potassium (mmol/L)	3.80 ± 0.66	4.27 ± 3.49	0.329
Urea (mmol/L)	4.94 ± 3.05	3.87 ± 2.22	0.009
Creatinine (mmol/L)	36.17 ± 13.1	40.07 ± 11.04	0.046

All data are displayed as mean ± standard deviation; CRP, C-reactive protein.
* Derived from Student's T-test.

the child's age, the risk of contracting a rotavirus infection increases as an unwelcome consequence.

The diarrhoea in a rotavirus infection is both osmotic and secretory in nature. The osmotic diarrhoea occurs as a result of maldigestion and malabsorption of nutrients, consequent to either enterocyte damage or death, or to reduce epithelial absorptive capacity.[6,11] The rotavirus secretory diarrhoea on the other hand is orchestrated by non-structural protein 4 (NSP4) which acts as an enterotoxin.[6] Contrary to the bloody diarrhoea (also known as dysentery) caused by certain bacterial pathogens such as *Shigella* spp., *Salmonella* spp. and *Campylobacter* spp., the diarrhoea attributed to rotavirus is typically non-bloody.[6,12] However, the absence of bloody diarrhoea does not necessarily rule in RG because other viral pathogens (i.e., noroviruses, astroviruses and enteric adenoviruses) also cause non-bloody diarrhoea.[13] Thus, although diarrhoea is the most reported symptom in RG, its utility as a stand-alone symptom to diagnose the infection is poor. This finding of ours echoes that of a British study which also found a high prevalence of diarrhoea in RG (86%) that did not reach statistical significance.[14]

Unlike diarrhoea, vomiting is considered a central nervous system (CNS)-driven symptom. Rotavirus is hypothesised to exert its CNS effect via several non-mutually exclusive mechanisms. In the first mechanism, the release of mediators such as the rotavirus non-structural protein 4 (NSP4) stimulates adjacent intestinal enterochromaffin cells to liberate serotonin (or 5-hydroxytryptamine) that activates enteric neurons as well as vagal afferents that project to regions of the brain associated with nausea and vomiting.[6,15] In a host with blood-brain barrier dysfunction (which can result from either malnutrition or immunodeficiency) the virus can invade the brain to have a direct effect on it or replicate and bring about neurotransmitter dysregulation.[15] Alternatively, rotavirus may enter the lymphatic system first before disseminating to the CNS.[16] To further aggravate matters, delayed gastric emptying is known to be associated with rotavirus infection.[6] Our study has shown that compared to NRG, vomiting is indeed a statistically significant clinical characteristic of RG, a finding shared with that of a Vietnamese study.[17]

Like most infections, fever is also a prominent symptom of a rotavirus infection. While the precise mechanism of how a rotavirus infection can induce fever is undetermined, children with RG have been found to have raised levels of certain cytokines (i.e., interleukin-1β interleukin-6 and tumor necrosis factor alpha) in their sera compared to children without AGE.[6] These cytokines stimulate brain endothelial cells to produce prostaglandins which elevate body temperature through various heat-generating events, such as vasoconstriction, shivering, and alteration in the metabolic rate of peripheral cells.[18] It is important to note that other gastrointestinal pathogens (e.g. noroviruses) also stimulate the release of these same cytokines.[18] While the majority of our RG patients did present with fever (57%), the proportion of NRG patients with fever was significantly higher (76%). This contrasts with the finding of the British study, in which significantly more children with rotavirus-positive gastroenteritis had fever (p-value of 0.005).[14] One plausible explanation for this discrepancy is that the caretakers of our patients could have under-reported fever (particularly low-grade fever) without the aid of a thermometer as it is not as visible a sign as diarrhoea or vomiting, and the patients themselves may be too young to report it.

Convulsions are a neurological manifestation that has been reported to occur in 1-8% of children with RG.[19] These are commonly generalised, tonic-clonic seizures that occur in the absence of fever but carry a favourable prognosis.[20] Although the precise mechanism of convulsions in the setting of a rotavirus infection is elusive, it has been hypothesised that the virus may invade the brain following hematogenous spread through the blood-brain or the blood-CSF barrier, or after gaining access to the vagus nerve (or other peripheral nerves).[19] The absence of convulsions in our rotavirus cohort could be due to the inherent rarity of this specific presentation (i.e., as low as 1%) coupled with the relatively small sample size of our rotavirus patients. Its occurrence in our NRG patients could be the result of febrile seizures. Even in the absence of rotavirus infection, high-grade fevers accompanying diarrhoeal syndromes may induce febrile seizures since children <5 years old are highly vulnerable to febrile stimuli due to their central nervous system immaturity.[20]

Keeping in mind that vomiting is a more prominent symptom in RG compared to NRG, it is not surprising that clinical dehydration is more likely to be a feature of the former. This finding of ours echoes that of the Vietnamese study which reported an even lower p-value

of <0.001 favouring dehydration in RG.[17] This is reflected in the statistically higher mean serum urea level in children with RG. Unlike creatinine, serum urea concentration is affected by an individual's intravascular volume status – volume depletion augments the reabsorption of urea by the renal tubules which in turn increases the urea concentration in the plasma.[21] Although our study's mean serum urea level of 4.9 mmol/L still within the normal reference range for this analyte, the British study reported a much higher mean level of 5.9 mmol/L in RG.[14] Thus, the measurement of serum urea in a clinically dehydrated child with AGE should be undertaken as it will strengthen the suspicion of a rotavirus infection if its level is elevated.

CRP is a biomarker synthesised by the liver. Its level typically rises during inflammation and it is regarded as the prototype acute-phase reactant protein. Unlike bacterial diarrhoeal syndromes, rotavirus infection results in a limited inflammatory response, which is reflected in nearly unaltered CRP levels in children with RG.[6] German investigators have found that children with rotavirus infection tended to have CRP levels below 2.3 mg/dL.[22] While the mean CRP level of our RG patients (i.e., 0.86 mg/dL) was slightly above our center's normal reference range of 0.5 mg/dL, it was still much lower than the cutoff proposed by the German study, essentially validating the notion that inflammation is restricted in rotavirus infections. Another frequently used indicator for inflammation, the total white cell count (TWBC), appears to be of limited value in distinguishing RG from NRG because despite a lower mean cell count in RG, the association was not statistically significant. This is in accordance with the low reported sensitivity (i.e., 67%) of TWBC in detecting rotavirus infection.[23]

In conclusion, although RG shares a key similarity with AGE caused by other pathogens by having diarrhoea as the most prominent presentation, children with RG are more likely to present with vomiting and therefore dehydration. Accordingly, the serum urea levels in RG patients are likely to be elevated. A normal or only marginally raised blood CRP level will further raise the probability of RG.

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